AMENDMENTS TO THE CLAIMS

Applicant presents a full set of claims showing markups of the claims with insertions and deletions indicated by underlining and strikethrough text (or double bracketing), respectively.

1. (Original) A genetically modified non-human mammal or cell characterised in that it does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide and in that one or more endogenous Ig H Variable region, one or more endogenous Ig H D segment, and one or more endogenous Ig H J segment nucleic acid sequences are present.

2. (Original) A genetically modified non-human mammal or cell characterised in that it does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region locus polypeptide and in that all the endogenous Ig H Variable region, D and J segment nucleic acid sequences are present.

3. (Previously presented) A genetically modified non-human mammal or cell according to claim 1 characterised in that it does not comprise a nucleic acid sequence which itself encodes any immunoglobulin heavy chain constant region (IgH C) polypeptide.

4. (Previously presented) A genetically modified non-human mammal or cell according to claim 1 characterised in that all immunoglobulin heavy chain constant region gene sequences are absent or partially absent from the genome.

5. (Previously presented) A genetically modified non-human mammal or cell according to claim 1, characterised in that it is obtainable or obtained by targeted deletion of essentially all endogenous IgH C gene sequences.

6. (Previously presented) A genetically modified non-human mammal or cell according to claim 1 characterised in that it is obtainable or obtained by Cre *lox*P recombination.

7. (Previously presented) A genetically modified non-human mammal or cell according to claim 1 characterised in that at least part of at least one IgH C gene enhancer sequence is present.

8. (Previously presented) A genetically modified non-human mammal or cell according to claim 1 characterised in that a non-endogenous site-specific recombination sequence is present within the genome.

9. (Withdrawn) A genetically modified non-human mammal or cell characterised by having a non-endogenous site-specific recombination sequence downstream of, or within the last gene of the IgH C locus.

10. (Withdrawn) A genetically modified non-human mammal or cell according to claim 8 characterised by having a further non-endogenous site specific recombination sequence upstream of, or within the first gene of the IgH C locus.

11. (Previously presented) A genetically modified non-human mammal or cell according to claim 1 characterised in that one or more selectable marker(s) is present within the genome.

12. (Original) A genetically modified non-human mammal or cell according to claim 8 characterised in that at least one selectable marker is present upstream of, or downstream of, the non-endogenous site specific recombination sequence.

13. (Withdrawn) A genetically modified non-human mammal or cell according to claim 9 characterised in that at least one selectable marker is integrated within the genome upstream of, and/or downstream of, at least one non-endogenous site specific recombination sequence.

14. (Previously presented) A genetically modified non-human mammal or cell according to claim 11 characterised in that the selectable marker(s) is one or more selectable marker selected from a group comprising a neomycin resistance gene, a puromycin resistance gene, and a hygromycin resistance gene.

15. (Currently amended) A genetically modified non-human mammal or cell according to claim 8 [[7]] characterised in that the non-endogenous site-specific recombination sequence is a *lox*P site.

16. (Previously presented) A genetically modified non-human mammal according to claim 1 characterised in that it is a mouse.

17. (Withdrawn) A genetically modified non-human cell according to claim 1 characterised in that it is a mouse cell.

18. (Previously presented) A genetically modified mouse according to claim 16, characterised in that all eight endogenous IgH C genes μ, δ, γ3, γ1, γ2a, γ2b, ε and α are absent or partially absent.

19. (Withdrawn) A genetically modified non-human cell according to claim 1 characterised in that it is an embryonic stem cell.

20. (Previously presented) A genetically modified non-human mammal derived from a genetically modified non-human mammal of claim 1.

21. (Withdrawn) A genetically modified non-human mammal derived from a genetically modified non-human cell of claim 1.

22. (Previously presented) A genetically modified non-human cell derived from a genetically modified non-human mammal of claim 1.

23. (Withdrawn) A method for producing a genetically modified non-human cell comprising:

(a) (i) transfecting a non-human cell with a targeting construct for integration upstream of, or within the first IgH C gene of the IgH C locus, said targeting construct comprising a non-endogenous site specific recombination sequence and a selectable marker, selecting for a cell in which the selectable marker is present and screening said cell for integration of the recombination sequence, and,

(ii) transfecting a cell produced in (a)(i) with a targeting construct for integration downstream of, or within the last IgH C gene of the IgH C locus, said targeting construct comprising a selectable marker and a non-endogenous site-specific recombination sequence, selecting for a cell in which the selectable marker is present and screening said cell for integration of the recombination sequence; or

(b) (i) transfecting a non-human cell with a targeting construct for integration downstream of, or within the last IgH C gene of the IgH C locus, said targeting construct comprising a non-endogenous site-specific recombination sequence and a selectable marker selecting for a cell in which the selectable marker is present, and screening said cell for integration of the recombination sequence, and

(ii) transfecting a cell produced in (b)(i) with a targeting construct for integration upstream of, or within the first IgH C gene of the IgH C locus, said targeting construct comprising a non-endogenous site-specific recombination sequence and a selectable marker, selecting for a cell in which the selectable marker is present, and screening said cell for integration of the recombination sequence; or

(c) co-transfecting a non-human cell with a targeting construct for integration upstream of, or within the first IgH C gene of the IgH C locus and with a targeting construct for integration downstream of, or within the last IgH C gene of the IgH C locus, each of said targeting constructs comprising a non-endogenous site specific recombination sequence and each having a selectable marker, selecting for a cell in which the selectable marker(s) is/are present, and screening said cell for integration of the recombination sequence; and optionally,

(d) providing to a cell obtained in (a)(ii), (b)(ii) or (c) a recombinase active at the non-endogenous site-specific recombination sequence and, optionally, screening for deletion events.

24. (Withdrawn) A method according to claim 23 characterised in that the non-endogenous site-specific recombination sequence is a *lox*P site.

25. (Withdrawn) A method according to claim 24 characterised in that, in optional step (d), the recombinase is a Cre recombinase.

26. (Withdrawn) A method according to claim 23 characterised in that the recombinase is provided by an expression vector.

27. (Withdrawn) A method according to claim 23 characterised in that the genetically modified non-human cell is a mouse cell.

28. (Withdrawn) A method according to claim 23 characterised in that the genetically modified non-human cell is an embryonic stem cell.

29. (Canceled)

30. (Withdrawn) A method for producing a genetically modified non-human mammal characterised in that an embryonic stem cell of claim 19 is introduced into a host blastocyst and developed into a chimaeric animal.

31. (Withdrawn) A method for producing a genetically modified non-human mammal characterised by:

(a) introducing a non-human mammal embryonic stem cell according to claim 19 into a compatible non-human mammal blastocyst, and

(b) transplanting the blastocyst obtained in (a) into a compatible non-human mammal foster mother to obtain a chimaeric non-human mammal, and optionally, screening for the selectable marker(s), and/or the non-endogenous site specific recombination sequence(s), and/or for deletion of essentially all endogenous IgH C gene sequences.

32. (Withdrawn) A method for producing a genetically modified non-human mammal characterised in that the chimaeric non-human mammal according to claim 30 is bred to obtain heterozygous progeny.

33. (Withdrawn) A method for producing a genetically modified non-human mammal characterised in that the heterozygous progeny of claim 32 is inter-bred to obtain homozygous progeny.

34. (Withdrawn) A method for producing a genetically modified non-human mammal characterised by cross-breeding a genetically modified non-human mammal homozygous for integration of a non-endogenous site-specific recombination sequence upstream of, or within the first IgH C gene of the IgH C locus with a compatible genetically modified non-human mammal homozygous for integration of a non-endogenous site-specific recombination sequence downstream, or within the last IgH C gene of the IgH C locus, to obtain heterozygous progeny and optionally interbreeding the heterozygous progeny to obtain progeny homozygous for both integrations.

35. (Withdrawn) A method according to claim 34 characterised by further comprising cross-breeding progeny homozygous for both integrations with a compatible non-human mammal capable of expressing a recombinase active at the non-endogenous site specific recombination sequence to obtain progeny; and optionally screening the progeny obtained for IgH C gene deletion.

36. (Withdrawn) A method according to claim 34 characterised in that the non-endogenous site specific recombination sequence(s) are *lox*P sites.

37. (Withdrawn) A method according to claim 36 characterised in that the recombinase is a Cre recombinase.

38. (Withdrawn) A method according to claim 36 characterised by further comprising cross-breeding progeny heterozygous or homozygous for *lox*P at both loci with a compatible non-human mammal capable of expressing Cre recombinase to obtain a progeny non-human mammal that does not comprise a nucleic acid sequence which itself encodes any endogenous Ig heavy chain constant region polypeptide on one or both alleles.

39. (Previously presented) A genetically modified non-human mammal characterised in that it is obtainable or obtained by a method of claim 35 and does not comprise a nucleic acid sequence which itself encodes any endogenous Ig heavy chain constant region polypeptide and

in that one or more endogenous Ig H Variable region, one or more endogenous Ig H D segment, and one or more endogenous Ig H J segment nucleic acid sequences are present.

40. (Previously presented) A genetically modified non-human mammal characterised in that it is obtainable or obtained by a method of claim 35 and does not comprise a nucleic acid sequence which itself encodes any endogenous Ig heavy chain constant region polypeptide and that all the endogenous Ig H Variable region, D and J segment nucleic acid sequences are present.

41. (Withdrawn) A method for producing a genetically modified non-human mammal capable of expressing one or more exogenous genes, characterised by breeding a genetically modified non-human mammal according to claim 1 that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide, with a compatible non-human mammal that encodes and is capable of expressing one or more exogenous gene(s), to obtain progeny heterozygous for the one or more exogenous gene(s), and optionally inter-breeding the heterozygous progeny to produce progeny homozygous for the one or more exogenous gene(s).

42. (Withdrawn) A method for producing a genetically modified non-human mammal or cell capable of expressing one or more exogenous gene(s) characterised by comprising introduction of one or more exogenous gene(s) into a non-human mammalian cell according to claim 1 that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide.

43. (Withdrawn) A method according to claim 42 characterised in that the non-human mammalian cell is an embryonic stem cell.

44. (Withdrawn) A method according to claim 43, characterised in that the one or more exogenous gene(s) are introduced by transfection.

45. (Withdrawn) A method according to claim 42 characterised in that the non-human mammal cell is an oocyte (egg cell).

46. (Withdrawn) A method according to claim 45, characterised in that the one or more exogenous gene(s) are introduced by DNA micro-injection.

47. (Withdrawn) A method according to claim 42 characterised in that the one or more exogenous gene(s) are inserted into the genome of the non-human mammal or cell.

48. (Withdrawn) A method according to claim 47 characterised in that the one or more exogenous gene(s) are inserted into a non-endogenous site specific recombination sequence.

49. (Withdrawn) A method for producing a genetically modified non-human mammal capable of expressing one or more exogenous gene(s) characterised by cross-breeding a non-human mammal that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide and in that one or more endogenous Ig H Variable region, one or more endogenous Ig H D segment, and one or more endogenous Ig H J segment nucleic acid sequences are present with a transgenic mammal having one or more exogenous gene(s) associated with or flanked by a non-endogenous site specific recombination sequence and having a recombinase active at the non-endogenous site specific recombination sequence to obtain progeny and optionally screening the progeny for insertion of the one or more exogenous gene(s).

50. (Withdrawn) A method for producing a genetically modified non-human mammal capable of expressing one or more exogenous gene(s) characterised by cross-breeding a non-human mammal that does not comprise a nucleic acid sequence which itself encodes any endogenous immunoglobulin heavy chain constant region polypeptide and in that all the endogenous Ig H Variable region, D and J segment nucleic acid sequences are present with a transgenic mammal having one or more exogenous gene(s) associated with or flanked by a non-endogenous site specific recombination sequence and having a recombinase active at the non-endogenous site specific

recombination sequence to obtain progeny and optionally screening the progeny for insertion of the one or more exogenous gene(s).

51. (Withdrawn) A method according claim 46 characterised in that the non-endogenous site specific recombination sequence is a *loxP* sequence and insertion is by Cre – *lox P* integration.

52. (Withdrawn) A method according to claim 41 characterised in that the genetically modified non-human mammal is a mouse.

53. (Withdrawn) A method according to claim 41 characterised in that the exogenous gene or genes is an Ig H gene or Ig H genes.

54. (Withdrawn) A method according to claim 53 characterised in that the Ig H gene or genes is an IgH C gene or IgH C genes.

55. (Withdrawn) A method according to claim 41 characterised in that the exogenous genes or genes are a human gene or human genes.

56. (Withdrawn) A method according to claim 41 characterised in that the exogenous genes are a human Ig heavy chain locus having V, D, J and/or C regions.

57. (Withdrawn) A method according to claim 56 wherein the human Ig heavy chain locus V, D, J and/or C regions are in germline configuration.

58. (Withdrawn) A method according to claim 56 wherein the human Ig heavy chain locus V, D, J and/or C regions are productively arranged.

59. (Withdrawn) A non-human mammal or cell obtainable by a method of claim 41.

60.-61. (Canceled)

62. (Withdrawn) A method for production of exogenous immunoglobulin comprising use of a non-human mammal or cell according to claim 59.

63. (Withdrawn) A method for production of human immunoglobulin comprising use of a non-human mammal or cell according to claim 59.

64. (Withdrawn) A method according to claim 62 wherein the non-human mammal is a rodent.

65. (Withdrawn) A method according to claim 62 wherein the non-human mammal is a mouse.

66. (Withdrawn) A method according to claim 62 wherein the non-human cell is a rodent cell.

67. (Withdrawn) A method according to claim 62 wherein the non-human cell is a mouse cell.

68. (Withdrawn) An immunoglobulin obtainable or obtained by a method according to claim 62.

69. (Withdrawn) A human immunoglobulin obtainable or obtained by a method according to claim 62.

70.-71. (Canceled)

72. (Withdrawn) A medicament composition comprising an immunoglobulin according to claim 68 and a pharmaceutically acceptable excipient.

73. (Withdrawn) A genetically modified mouse cell according to claim 17, characterised in that all eight endogenous IgH C genes μ, δ, γ3, γ1, γ2a, γ2b, ε and α are absent or partially absent.